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#### REMARKS

This amendment is responsive to the Office Action mailed July 30, 2003 (hereinafter the "present Office Action"). Original claims 17-48 are under examination in the present action. Claims 17-22, 28 and 29 stand rejected. Claims 23-27 and 30-48 have been withdrawn from consideration. Reconsideration of the present Office Action and allowance of the application, as amended, are respectfully requested.

1. In response to the Examiner's request detailed in paragraph 1 of the present Office Action, Applicant has canceled claims 33 - 48, without waiver or prejudice, with the expressed reservation to file a subsequent application, as provided for by 35 U.S.C. 121, directed to the canceled claims.

2. The Examiner notes that the pending claims are inconsistent with the elected invention. In an effort to conform the pending claims with the elected invention and species, claim 25 has been amended to depend on claim 22.

3. The Examiner objects to the Abstract of the Invention as being not descriptive. In response thereto, Applicant requests the entry of the above amended Abstract of the Invention which specifically states that the claimed invention is directed to an oil-in-water process for preparing controlled-release biodegradable microspheres

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and/or nanospheres containing bioactive peptides which involves preparing a solution of the bioactive peptide complexed with an anionically or cationically functionalized biodegradable polyester in an organic solvent. Applicant submits that the proposed Abstract is consistent with the elected invention.

4. Applicant acknowledges the transfer the Sequence Listing from the parent application to the present application and is appreciative of the Examiner's efforts.

5. The Examiner rejected claims 20 and 29 as being broader in scope than the base claim that they are dependent thereon. Applicant has amended claims 20 and 29 to replace the broader "polymer" with "polyester" as directed by the Examiner. In addition, Applicant has amended claim 21 in the same manner for the same reasons, although not specifically objected to.

***Response to issues presented under 35 U.S.C. §103***

5 (2<sup>nd</sup> occurrence). Claims 17-22, 28 and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 5,635,216 issued to Thompson et al. (hereinafter referred to as "Thompson") in view of U.S. 4,383,975 issued to Fong (hereinafter referred to as "Fong"). Specifically, the Examiner contends that Thompson teaches the same oil-in-water process to prepare polyester microparticles containing

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bioactive peptide as does the present application with the exception that it does not specifically teach the use of sodium oleate as the preferred surfactant. The Examiner states that Fong, however, demonstrates the advantages of using the preferred surfactant in similar oil-in-water processes and that it "would have been quite obvious to one skilled in the art at the time the invention was made" to use sodium oleate in the process discussed by Thompson.

Applicant respectfully directs the Examiner's attention to the first step of the claimed process of the present application wherein it is unambiguously stated that a salt of a peptide complexed with an anionically or cationically functionalized biodegradable polyester is **dissolved** in an organic solvent to form **a solution**. Thompson, on the other hand, involves the preparation of a **suspension**, not a solution. See Thompson column 5, lines 31-32; column 7, lines, 4 and 45; column 8, lines 15 and 60; column 9, line 33; column 10, lines 5 and 42; column 11, lines 11 and 47; and column 12, lines 16. Compare the process of the present application with the Abstract of Thompson which states that the claimed process involves "suspending a biologically active in the polyester solution." Applicant asserts that a suspension, which is a heterogeneous mixture composed of a

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diverse and continuous phase<sup>1</sup>, is not the same as a solution which is a homogeneous, single-phase mixture of two or more substances.

In further support thereof, Applicant directs the Examiner's attention to the Background of the Invention of the present application wherein Applicant readily admits that oil-in-water processes were known at the time the present application was filed, but that the known processes resulted in low encapsulation efficiency, especially when the peptide is present as a free base. Applicant respectfully asserts that the Thompson process was one of those flawed processes. In support thereof, directs the Examiner's attention to column 2, line 23 to 26 wherein it is reported that the Thompson process resulted in microparticles containing from 5% to 25% by weight a biologically active peptide. Compare that to page 6, line 14 of the present application, which states that "[t]he microspheres... made according to a process of this invention contain from less than 0.1% by weight up to approximately 50% by weight of a peptide." If the process of the present application were substantially similar to the Thompson process, one would expect the present process to produce

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<sup>1</sup> Applicant respectfully submits that the Thompson process does not utilize a peptide complexed with a functionalized biodegradable polyester. Complex ions result from the formation of coordinate covalent bonds between simple ions and other ions or molecules. The Thompson process, therefore, does not involve dissolving such a complex which is a crucial step in the claimed process of the present application.

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microparticles containing 25% by weight of the peptide. Microparticles comprised of up to 50% by weight of a biologically active peptide would not be expected. It is well-established principle that extrinsic evidence, such as unexpected results, bolsters the nonobvious nature of the claimed invention. *Graham v. John Deere Co.*, 38 U.S. 1, 148 U.S.P.Q. (BNA) 459 (1966).

The Examiner recognizes that the Thompson reference does not specifically teach the elected species of surfactant, sodium oleate, but that Fong does, and as such, the claimed process is obvious. Assuming *arguendo* that but for disclosing the preferred surfactant the Thompson process is patentably indistinguishable from the process of the present application, obviousness cannot be established by combining Thompson with Fong absent some teaching, suggestion or incentive supporting the combination.

"[A] proper analysis under §103 requires, *inter alia*, consideration of . . . whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed invention", *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success."; *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442

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(Fed. Cir. 1991). Applicant respectfully contends that Fong does not provide such motivation and as such does not correct the deficiency present in Thompson. Applicant respectfully contends that the claimed process of the present application is patentably distinct from the process disclosed by Thompson or Fong.

Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 17 - 22, 28 and 29 under 35 U.S.C.103(a) as obvious over Thompson in view of Fong.

***Response to issues presented under 35 U.S.C. §103***

6. Claims 17-22, 28 and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 5,445,832 issued to Orsolini et al. (hereinafter referred to as "Orsolini") in view of U.S. 5,672,659 issued to Shalaby et al. (hereinafter referred to as "Shalaby") in further view of U.S. 4,383,975 issued to Fong (hereinafter referred to as "Fong"). Specifically, the Examiner contends that Orsolini teaches the conversion of a peptide into a water-insoluble salt prior to preparing microcapsules using a similar oil-in-water process as disclosed in the present application. The Examiner recognizes that Orsolini does not recognize the inherent benefits of using water-insoluble complexes of

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peptides with anionically functionalized polyesters<sup>2</sup>. The Examiner states that Shalaby, however, teaches a method of preparing microcapsules containing peptides and polyesters having one or more free COOH groups<sup>3</sup>. The Examiner opines that "one skilled in the art at the time the invention was made would be motivated to use peptide conjugates of Shalaby instead of the peptide salts of Orsolini in preparing microcapsules for sustained and controlled release of peptides." The Examiner also recognizes that Orsolini does not suggest the use of the elected surfactant, sodium oleate. The Examiner argues, however, that "one would" be motivated "to use sodium oleate as a surfactant" based on Fong.

Like Thompson, Orsolini employs a suspension in its process to produce microspheres of biodegradable material and as such, Orsolini is no more relevant than Thompson was with respect to the determination of the "obviousness" of the claimed process. See Orsolini column 1, lines 21-22; column 2, lines 12-14; column 3, lines 41-44; and column 4, line 59. Applicant adopts and reasserts all of the arguments made previously with respect to Thompson against Orsolini.

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<sup>2</sup> The Examiner does not address the possibility that the peptide is complexed with a cationically functionalized polyester, as recited in generic claim 17.

<sup>3</sup> The Examiner does not allege that Shalaby discloses cationically functionalized polyesters and as such does render such complexes obvious.

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Extrinsic evidence supporting the nonobviousness of the claimed process can be found in Orsolini. As stated on page 3 at line 5 of the present application, an important feature in the encapsulation of water soluble peptides is the encapsulation efficiency, which is defined as the amount of peptide actually present in the microspheres compare to the amount initially used in the process. See Specification of the present application at page 17, lines 2-4. As stated on page 6 of the present application, encapsulation efficiencies greater than 85% can be achieved using the method of the present application.

Comparing encapsulation efficiencies, the method of the present application is far superior to that of the method of Orsolini. Orsolini reported that for Example 1 the yield of microspheres was 63% and the loading of peptide was 9.05% compared to the calculated figure of 10%. The encapsulation efficiency for Example 1 of Orsolini is calculated as follows:  $63 \times 9.05 \div 10 = 57\%$ . Results for the other examples are given below:



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Example	Encapsulation Efficiency
2	60.7%
3	14.9%
4	53.5%
5	52.9%
6	72.8%

The improvement in encapsulation efficiency of the process of the present application support the nonobviousness of the instant invention. As stated previously, under *Graham*, evidence of an improvement over the prior art is sufficient to overcome an obviousness finding. Reconsideration of the rejection is accordingly respectfully requested.

Assuming *arguendo* that Orsolini did describe a process for making microcapsules that was patentably indistinct from the claimed process of the present application with the exception of, as identified by the Examiner, not using anionically functionalized polyesters or the preferred surfactant, sodium oleate, neither Shalaby nor Fong correct these deficiencies since neither teaches, suggests or provides incentive supporting the combination.

Applicant respectfully requests the reconsideration of the rejection of claims 17-22, 28 and 29 under 35 U.S.C. §103(a) as being unpatentable over Orsolini in view Shalaby and in further view of Fong.

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### ***Request for Rejoinder***

Applicant submits that claim 17 is a generic claim and based on the above arguments is in a condition for allowance. Upon the allowance of a generic claim, an Applicant is entitled to consideration of claims to additional species which are written in dependent form as provided for by 37 C.F.R. §1.141. Applicant respectfully requests that withdrawal of claims 23<sup>4</sup>, 24, 26<sup>5</sup> and 27<sup>6</sup> be rescinded and that said claims be reconsidered.

In summary, it is believed that the instant application is now in an allowable condition and such allowance is earnestly solicited.

Examiner Borin is invited to telephone the Applicant's representative at the telephone number indicated below to facilitate the prosecution of this application. The Commissioner is hereby authorized to charge any additional

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<sup>4</sup> Claims 23 and 24 are directed to the use of polyvinyl alcohol as a surfactant which was also employed as a "stabilizer" in Thompson.

<sup>5</sup> Claim 26 is directed to microspheres containing the LHRH analogue of the formula pyroGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH<sub>2</sub> which was also incorporated into the microspheres of Fong.

<sup>6</sup> Claim 26 is directed to use of polylactide-co-glycolide, polycaprolactone or polyanhydride which were also used in Thompson.

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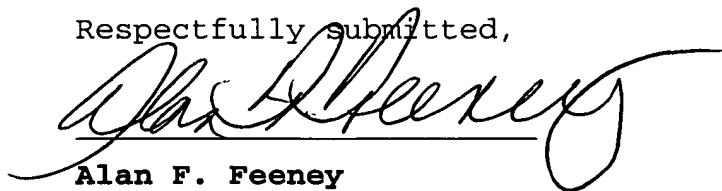
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Respectfully submitted,



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